Dear Senator Wyden and Senator Grassley,

I read your report on the pricing of Sovaldi and Harvoni with great interest. Your team has done a remarkable job putting together so many internal documents and testimonials, and bringing to the public eye the inner workings and decision-making process of a pharmaceutical company. On the other hand, for me as a professional that consults for biotechnology and pharmaceutical firms on a variety of commercial topics, the report contained few surprises. I would like to try to connect the industry perspective with the sentiments expressed in the report in order to find answers for the questions posed in your letter to the public.

Profit maximization vs patient access

One of the key conclusions of the report was that "in considering how to price its drugs, Gilead prioritized revenue and profit maximization over patient access". This has been condemned as immoral in some of the press statements, such as the one from Senator Wyden: "Gilead pursued a calculated scheme… regardless of human consequences"[1]. However, an impassionate observer would ask why the public would expect a private company to be acting as a charitable institution. New cars are equipped with additional safety features that may save one's life, but nobody is demanding that Honda or Ford sell their new models at a more affordable price.

Certainly, drugs are not exactly equivalent to cars in terms of their importance to human well-being. That is the reason for the increased scrutiny that drug-makers are subjected to. Pressure from advocacy groups as well as internal ethical considerations do play a role in the decision-making today, as can be illustrated by, for example, speedy development of Ebola vaccine in response to the recent epidemic by such companies as GSK and Merck (e.g. Forbes estimated Merck's annual revenues from a hypothetical Ebola vaccine at $40-$50 million, and costs of development at $200-$500 million[2]). However, it is not reasonable to expect this to become the guiding principle for a company, as such strategy will clearly not be sustainable.

As we were taught in Economics 101, companies as well as individuals respond to incentives. Profit maximization is usually one of the top incentives for any private company, its *modus vivendi*. In the drug development business incentives are also shaped by the regulatory environment. A prime example of the impact of regulations is the Orphan Drug Act (ODA). Introduced in 1983, it provided a variety of incentives, including tax credits, fee waivers, market exclusivity etc., for developing drugs for orphan diseases (those affecting less than 200,000 patients in the US)[3]. While on average ~2 orphan drugs were approved before the introduction of the ODA, this number increased to ~7 over the next 30 years (with as many as 18 orphan drugs approved in 2014)[3]. This example illustrates that in order to understand and influence the motivation and strategy of the drug companies one has to understand the set of incentives governing their behavior today.

[1] http://time.com/money/4131750/senate-blames-greed-1000-hepatitis-c-drug-sovaldi/
[2] http://www.forbes.com/sites/greatspeculations/2015/08/24/mercks-ebola-vaccine-wont-move-the-needle/#50acc844437a
[3] https://rarediseases.org/assets/files/white-papers/2015-06-17.nord-bio-ey-odtc

What role does the concept of "value" play in the debate, and how should an innovative therapy's value be represented in its price?

This question was listed as #3 in your letter, but I would like to address it first as the most fundamental of all, in my opinion. Indeed, criticism of the pricing practices of the pharma companies has intensified recently, especially in the wake of Turing Pharma scandal. Several high-profile figures, including presidential candidates, have proposed to address this issue by tying drug price to the cost of development. One of the conclusions of your report was the fact that costs did not really play into Gilead's pricing decisions.

In my view, the idea of linking drug prices to development costs is dangerous and detrimental to innovation. Indeed, what kind of incentive would such a law provide? It would encourage companies to increase their upfront costs in order to justify higher prices in the future (assuming the price is to allow some fixed margin above the cost – thus higher costs will results in higher profit margins). This is the opposite of what any "normal" company wants to do, i.e. minimize costs. Moreover, the focus on costs shifts attention away from what really matters, and that is the value that a drug can provide. We would not pay a high price for a car that is made of expensive components but that cannot be driven - why should we do this for a drug?

The concept of "value" for a drug is a matter of debate; however, there is a fairly well-established literature on the measurement of the value of drugs and other medical interventions. Quantities such as QALYs (quality-adjusted life years) and DALYs (disability-adjusted life years) are widely used, including by such respected organizations as WHO[4] and NICE[5]. Other frameworks are also being developed (e.g. by ASCO[6]). The need for such metrics stems from basic economics: our resources are finite, and thus we cannot make everybody infinitely healthy, even if we wanted to. Philosophically, one can also argue that it is not fair, as increasing expenditures in healthcare will entail reduction of expenditures in other areas, such as education. Education has a variety of benefits associated with it (including, in correlation, better health[7]). Individuals can express preferences over their health states, and can compare the benefits of different types of medical interventions, or even medical and non-medical interventions or events.

Value is thus a crucial element that is often missing from the debate. Importantly, value is largely missing from the current system of incentives that companies in the US are exposed to. FDA approves drugs based on safety and efficacy alone, and no other centralized body can make decision about the relative value of new treatments (unlike said NICE in UK). It is true that in the US insurance companies, PBMs (pharmacy benefit managers) and certain government agencies such as VA and Medicaid do participate in negotiations with the companies regarding drug pricing. However, due to fragmentation their power is limited (as was outlined in your report). Moreover, in the absence of established value metrics the typical approach that companies use for pricing assessment is "analog analysis": when a qualitative comparison is made between the new drug and existing treatments, and price of the new treatment is set based on prior benchmarks (as also described in the report). However, this approach is deeply flawed, since (a) the price of the old treatments was not necessarily set in connection with their

[4] http://www.who.int/quantifying_ehimpacts/publications/en/9241546204chap3.pdf
[5] http://publications.nice.org.uk/how-nice-measures-value-for-money-in-relation-to-public-health-interventions-lgb10b/nices-approach-to-economic-analysis-for-public-health-interventions
[6] http://www.asco.org/practice-research/value-cancer-care
[7] http://www.npc.umich.edu/publications/policy_briefs/brief9/

objective value, and (b) drugmakers in the US take regular price increases, resulting in constant price inflation[8] (this is partially mitigated by increased discounts to the payors).

As a result, the current system is not very efficient. While true innovation is rewarded (and Sovaldi is an example of true innovation), the price paid may not be related to the value provided. Additionally, new drugs may appear on the market, whose incremental value over existing treatments is minuscule or non-existent, but that are priced highly based on the "analog" approach. One can argue that better incentives are needed that will reward true innovation appropriately while discouraging development of lesser value drugs. This will reduce the burden on the healthcare system and optimize resource allocation of the private sector. The exact definition of "value", however, has caveats, as we will see from the discussion below.

What are the effects of a breakthrough, single source innovator drug on the marketplace?

While the discussion of value is of great importance to the overall structure of the pharmaceutical market in the US, the case of Sovaldi has some specifics that require additional considerations. Namely:

1. Sovaldi is an example of a truly innovative drug, offering significantly better efficacy, fewer side effects and added convenience over the standard of care in Hepatitis C
    a. In particular, Sovaldi is offering a cure for HepC, something that few drugs for chronic conditions are capable of.
2. The eligible population for Sovaldi is very large, 3-5 million in the US[9]

The combination of highly effective (and thus relatively expensive) drug with large patient population was what really exposed the troubled foundation of the current system. Indeed, the price of Sovaldi per se, while high, does not look excessive when compared to other drugs on the market. For example, Alexion's Soliris for certain blood disorders costs ~$700,000 per year[10], Vertex's Kalydeco for a subpopulation of cystic fibrosis patients costs ~$300,000 per year[11], many oncology products costs upwards of $100,000[12]. And some of these drugs (e.g. Soliris and Kalydeco) have to be administered chronically, thus bringing lifetime costs to tens of millions (!) of dollars, as opposed to a single $84,000 payment in case of Sovaldi. So it's not surprising that when evaluated using the QALY methodology, Sovaldi is actually found to be cost-effective in most instances[13].

However, the crucial difference is in the eligible patient population. Soliris is used to treat paroxysmal nocturnal hemoglobinuria, an ultra-orphan disease with a prevalence of 1-5 per million[14] (thus 300-1,500 in the US). Similarly, Kalydeco is effective in a subset of cystic fibrosis patients numbering ~1,200 in the US[15]. Overall budget impact of each of these drugs on an annual basis is thus moderate, on the

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[8] http://www.wsj.com/articles/drugmakers-raise-prices-despite-criticisms-1452474210
[9] http://www.hepatitisc.uw.edu/pdf/screening-diagnosis/epidemiology-us/core-concept/all
[10] http://news.nationalpost.com/news/canada/worlds-most-expensive-drug-prescription-that-costs-up-to-700000-per-year-too-expensive-canada-says
[11] https://www.bostonglobe.com/business/2015/07/20/researcher-and-group-doctors-challenge-vertex-price-new-cystic-fibrosis-drug/d5PZMlj6T6uzq0usm2xLEL/story.html
[12] http://www.wsj.com/articles/the-art-of-setting-a-drug-price-1449628081
[13] http://blogs.wsj.com/pharmalot/2015/03/17/hepatitis-c-drugs-are-cost-effective-but-affordability-is-another-matter/
[14] http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2721357/
[15] http://www.natap.org/2011/newsUpdates/121911_02.htm

order of hundreds of millions of dollars. Interestingly, Hepatitis C prior to Sovaldi could also have been considered an orphan disease, as only 58,000 patients were treated (p. 12 of the report). However, the overall pool of eligible patients was much larger, and the number of treated expanded dramatically as Sovaldi was launched (figure on p. 10 of the report). As a result, annual budgets devoted to HepC ballooned to billions of dollars in a very short span of time, straining resources. In response, payers introduced restrictions to limit patient access and control costs. It should be noted that such restrictions also allowed resources to be used to treat other conditions, instead of spending all the money on Hepatitis C. In such a framework restrictions do not look as negative as some portray them – indeed, should we not try to save a cancer patient instead of spending money on a HepC patient with a mild form of the disease who could potentially wait till less expensive treatment come to the market?

What the discussion above is pointing to is a dilemma of health economics and health ethics that limits the applicability of the "value" concept as traditionally defined (see above). Indeed, if we value everybody's lives equally, a QALY for a cystic fibrosis sufferer should be treated equally to that of, say, diabetes patient. But since there are 25 million diabetic patients in the US and only ~30,000 cystic fibrosis patients, no company will be able to make a case for investing in cystic fibrosis over diabetes (assuming drug reimbursement is strictly tied to QALYs). While the ODA mentioned above did create regulatory incentives for companies to work in rare diseases, these developments likely would not have been possible without the ability of companies to set very high prices in order to justify their investments.

It is thus an ethical decision based on the consensus existing in a society to what extent the utility of the majority can be sacrificed to the utility of the minority. A pure utilitarian would likely argue for a strict equality – an extreme not supported today. But it is a fair question to ask how far the other way we as a society are prepared to go? And it is important to keep in mind that healthcare is not the only good that people value. A poor inner city kid today may live in squalid conditions, receive inadequate education, be surrounded by drugs and violence – but receive hundreds of thousands of dollars worth of healthcare. Is this an optimal solution?

<u>What measures might improve price transparency for new higher-cost therapies while maintaining incentives for manufacturers to invest in new drug development?</u>

To come back from the realm of ethics to specifics of drug pricing – what are possible mechanisms that will not only appropriately reward innovation, but also distribute resources in the most equitable way possible and avoid creating sudden excessive strains on the healthcare budgets? This is a question that a lot of people are struggling to find an answer to, so it would be naïve to expect to find one here. However, let me try to offer a couple of relevant thoughts.

1. It would be ideal if we can leverage the established theoretical approaches to calculating value of drugs (and in principle other medical interventions) as discussed above (leveraging the QALY framework)
2. Once the value of the drug is established, we need to make a decision on what a QALY is worth. As discussed above, our ethical standards (and economics of drug development) effectively preclude us from setting a constant price per QALY for all drugs, irrespective of the size of population

a. It is thus proposed to design a sliding scale of price/QALY as function of the eligible population: drugs targeted to a larger population will have a lower price/QALY compared to drugs for rare diseases
b. The specific functional form of this sliding scale will be determined by an independent commission with public input, ideally taking into account:
    i. Public health vs individual health priorities – how much more are we willing to spend to improve health of few people by the same amount as that of a large number of people
    ii. Benchmarking of other major budget items (e.g. can we calculate QALY for each additional year of schooling?)
    iii. Estimated costs of drug development
    iv. Length of patent protection (important to get a back-of-the envelope estimate of the total cash flow)
c. In my mind, items i. and ii. above should play a more important role than iii. and iv., since we don't want to peg innovation rewards solely to costs (and potentially inflate the latter). However, the cost side of the equation should provide a reality check as to whether proposed pricing is feasible
d. Several special cases need to be addressed
    i. If the population using a new drug is found to be significantly larger than expected initially, drug price should be reduced based on the same equation
    ii. If a highly effective drug for a large population is introduced to the market (like Sovaldi), it is still entirely conceivable that its impact on budgets will be heavy. To alleviate this issue, one can consider introducing annuity payments, where payments for a single patient are made over a course of time rather than immediately. This scheme is already being considered for cutting-edge curative treatments such as gene therapy
    iii. If the drug is approved in multiple indications with different efficacy, either a single weighted price can be used, or patient tracking according to diagnosis can be developed and tiered pricing implemented (the latter requires more sophisticated data analysis)
    iv. Price/QALY can be revised if the originator provides additional data on outcomes (e.g. if original approval was based on surrogate endpoints, but subsequently mortality data is made available)
e. Certainly, the above proposal is not straightforward. However, it is an attempt to inject scientific rigor and establish an ethical mandate for a field that is currently lacking both.

Sincerely yours,

Maxim Sheinin, Ph.D.

Life Sciences Consultant

Cambridge, MA